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The reaction of nitrosodicyclohexylamine with organolithiums

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The detailed study of the reaction of *N*-nitrosamines with organolithium compounds, under different reaction conditions, allowed the development of a useful methodology for the synthesis of substituted hydrazones and trialkyl hydrazines. The reaction proved to be very sensitive to the reaction conditions, and different main products can be obtained by fine tuning of several variables. With the purpose of searching into the reaction mechanism, a careful isolation, characterization, and quantitative determination of several minor products was carried out. *N*,*N*-dicyclohexylamine, *N*-cyclohexylidencyclohexyl amine, and *N*,*N*,*N*′-dicyclohexylalkylhydrazines, were the main side products identified after the work up of the reaction mixtures. With the same aim, the kinetics of the reaction of *N*-nitrosodicyclohexylamine with *n*-BuLi, was determined at temperatures in the range 0 °C room temperature. Under the conditions leading to the trialkyl hydrazine, the results show an abrupt slowdown of the reaction rate, after a short reaction time. This result, together with other observations, such as the recovering of hydrazone even when using high [RLi], is indicative of equilibrium involving different species in the reaction mixture. The isolation of reduction products, as well as additional experiments carried out with lithium dialkylamides and NO, allowed suggestion of an overall mechanistic scheme for the complex consecutive and parallel reactions, that is consistent with the afforded evidences. Copyright © 2008 John Wiley & Sons, Ltd.

Supporting information may be found in the online version of this article.

Keywords: nitrosamines; organolithiums; nitrosonium ions; hydrazones; hydrazines; denitrosation; reaction mechanism

INTRODUCTION

New reactions on nitrosamines are being actively studied specially on their relationship with carcinogenetic and mutagenic properties;[1] recent studies showed that they are mainly mutagenic through methylation of DNA.[2] There is special concern on the important roles that environmental nitrosamines play in the etiology of human cancer.[3] The tobacco-specific nitrosamine, (nicotine-derived nitrosamine ketone, NNK) found in cigarette smoke induces lung tumors in mice,[4] and esophageal and gastroduodenal cancer in animals,[5,6] nitrosamines have been also found in several food and beverages.[7–9]

On the other hand, hydrazones and hydrazines are receiving renewed interest due to the recent discovery of remarkable biological activities. These derivatives are well-known among pesticides, drugs, amino acid precursors, and synthetic building blocks for heterocyclic synthesis.[10] Several similar compounds were shown to be effective for the treatment of various diseases;[11] and hydrazine-based derivatives are found to be potent agents against hepatitis, AIDS, and SARS.[12,13] Some systematic synthetic methods have been recently developed, using protective group methodology, but they demand many steps (and the production of significant residues) for obtaining the end product;[14,15] development of cleaner tandem methodologies are desired.[16,17]

We recently reported the insertion of NO into the N—Li bond of lithium dialkylamides[18] and the present paper describes an extension of this reaction based on tandem additions of organolithium reagents. Mechanistic studies on the addition of RLi on a carbon–oxygen double bond are abundant in the literature, but few dealt with the addition of lithium amides.[19] The first adduct between an amine and a carbonyl derivative was isolated few years ago;[20] by ^{13}C NMR we characterized the first adduct between a formamide and R_2NLi,[21] and a more complex dilithiated adduct was lately characterized.[22] To the best of our knowledge, scarce studies dealt with the addition of RLi on a carbon–nitrogen double bond. The reaction described in this paper is extremely sensitive to the reaction conditions and precise determination of the reaction order was very difficult; nevertheless, the kinetic studies together with other evidences suggest the presence of complex equilibrium and competitive reactions.

RESULTS AND DISCUSSION

Alkyl additions to the N=O bond

The reaction of some organolithium compounds, R^1CH_2Li, with *N*-nitrosodicyclohexylamine, **1**, in THF, leads to the production of hydrazones, 2, as indicated in the Eqn (1)

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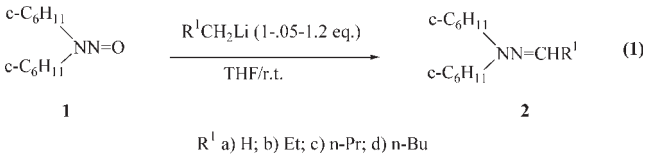
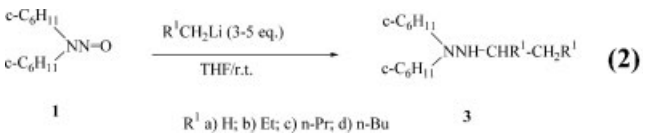


The reaction can be carried out at room temperature; in most cases the reaction time was very short (5 min, approx.). 1 mmol of **1** was dissolved in 2 ml of THF and the organolithium reagent was added in a $[R^1CH_2Li]$:[**1**] = 1.05–1.2 molar ratio. The concentration of organolithium was in the range 0.5–1.5 M approx., in *n*-hexane solution. In the case of MeLi, (that is less soluble in hexane) 1 M approx. THF solution was used, and a longer reaction time (2 h) was required. Table 1 summarizes the results. The reaction with PrLi (entry b) is particularly interesting, since the reaction is very clean and high yields are obtained. In the case of *n*-$C_5H_{11}Li$ (entry d), the yields are slightly lower likely due to the higher steric hindrance.

Tandem double alkylation

A second addition of another molecule of organolithium can be carried out in a tandem sequence starting from **1**. By carrying out the reaction of **1** with RLi, at room temperature, using a relatively high excess of RLi (Eqns (3)–(5)), a trialkyl hydrazine, **3**, is produced in good yields (Eqn (2))



In all cases the reactions were carried out in THF for 2 h at room temperature (runs at lower temperatures were not satisfactory). The results are shown in the Table 2. As can be observed, good yields of **3** were obtained for *n*-PrLi and *n*-BuLi (entries b and c). With *n*-$C_5H_{11}Li$, instead, lower yields of **3d** were obtained, and significant amounts of **2d** remained, likely the higher steric hindrance of the *n*-pentyl groups could be responsible for the lower reactivity. In the reactions with MeLi, normal addition to form the hydrazone of formaldehyde (**2a**) occurred; but when a second molecule of MeLi is added, loss of the elements of *lithium hydride* spontaneously occurs and the hydrazone of acetaldehyde, $(c\text{-}C_6H_{11})_2NN{=}CHCH_3$, is isolated as the main product instead of the trialkylhydrazine expected. A similar *LiH elimination* was early observed in the reaction of diethylnitrosamine with MeLi, for which a tiny amount (<2%) of $Et_2NN{=}CHCH_3$ was formed.[23] In good agreement with these observations, the yields of side products **4** and **5** are significantly higher than for the other RLi.

Table 1. Reaction of dicyclohexylnitrosamine, **1**, with RLi in THF at room temperature. Relative % yields of dicyclohexylalkylhydrazones, **2** and side products

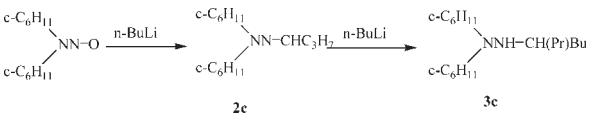
Entry	RLi[a]	R^1	% 2[b,c]	% 4[d]	% 5[e]	% 6[f]
a	MeLi	H	63[g]	5	6	1
b	*n*-PrLi	Et	93	—	7	—
c	*n*-BuLi	*n*-Pr	88	3	4	3
d	*n*-$C_5H_{11}Li$	*n*-Bu	69	6	12	—

[a] [RLi]:[**1**] = 1.05–1.2.
[b] **2**: $(C_6H_{11})_2NN{=}CHR^1$.
[c] No nitrosamine recovered.
[d] **4**: $(C_6H_{11})_2NH$.
[e] **5**: $(C_6H_{11})N(C_6H_{10})$.
[f] **6**: $(C_6H_{11})_2NNH\text{-}CH_2R^1$.
[g] 21% of **2c** observed.

Kinetic study

The reaction of **1** with organolithium compounds, carried out under the conditions previously mentioned renders the main products described. Nevertheless, the reaction leads also to the formation of some secondary products: dicyclohexylamine, **4**, *N*-cyclohexylidenecyclohexylamine, **5**, and *N,N,N′*-dicyclohexyl-*N,N′*-dicyclohexylalkylhydrazines, **6**, in low variable yields. It is interesting to comment the effect of adding more *n*-BuLi, after the reaction has advanced (i.e., when some remaining **2c** was still present in the reaction mixture), in experiments carried out under the conditions that lead to the formation of **3c** as the main product. In that cases, it was observed that a certain amount of the remaining **2c** could be converted to **3c**, although not completely. On the other hand, the amounts of **4**, **5**, and **6c** remained unchanged. These observations suggest the existence of chemical equilibria involving the *n*-BuLi and the species present in the reaction mixture, as it was reported before for other reactions involving lithium amides.[21,22,24]

To shed some light into the mechanism of this complex reaction a kinetic study was undertaken. The formation of **2c** (starting from **1**, and adding *n*-BuLi) is very fast (occurs in a few seconds, even at 0 °C), therefore, a kinetic study of the formation of this compound is difficult. In contrast, the formation of **3c** (at expenses of **2c**) is slower, and could be studied at low temperatures. A kinetic study of the formation of **3c** at different temperatures, starting from **1** and adding some excess of *n*-BuLi, was carried out. Under the conditions of this study, the hydrazone **2c** is formed *in situ*, and it reacts with more *n*-BuLi, affording **3c** (Eqn (3))



The reaction was followed by taking aliquots at different time intervals after the addition of *n*-BuLi, and analyzing the aliquots by GC. Tests were carried out at different temperatures and the results are shown in the Fig. 1. As can be observed, formation of **3c** is very fast at the beginning, but becomes very slow after nearly 20 min of reaction at room temperature (it is even slower at lower temperatures), remaining certain amounts of **2c**. This kinetic behavior, along with the observations commented above, could be indicative of a complex mechanistic scheme, involving equilibrium between the species and some lateral reactions.

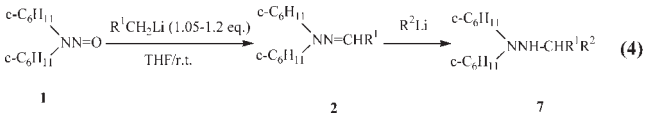
Table 2. Reaction of dicyclohexylnitrosamine, **1**, with RLi (in high excess) in THF, at room temperature. Relative % yields of trialkyl hydrazines, **3** and side products[a]

Entry	RLi	[RLi]:[1]	R^1	% 2[b]	% 3[c]	% 4[d]	% 5[e]	% 6[f]
a	MeLi	3	H	28	36[g,h]	11	8	4
b	*n*-PrLi	4	Et	9	77	3	1	2
c	*n*-BuLi	5	*n*-Pr	2	75	3	1	4
d	*n*-$C_5H_{11}Li$	8	*n*-Bu	13	61[i]	5	1	5

[a] Temperature: 20–25 °C. Reaction time 2 h.
[b] **2**: (c-$C_6H_{11})_2NN{=}CHR^1$.
[c] **3**: (c-$C_6H_{11})_2NNH$-$CH(R^1)R$.
[d] **4**: $(C_6H_{11})_2NH$.
[e] **5**: $(C_6H_{11})N(C_6H_{10})$.
[f] **6**: $(C_6H_{11})_2NNH$-CH_2R^1.
[g] The main product is (c-$C_6H_{11})_2NN{=}CHCH_3$.
[h] 9% of **2b**; side products 36% total yield.
[i] side products 26% total yield.

Reaction of nitrosamine, 1, with two different organolithium compounds

With the purpose of gaining more information into the mechanism of the reaction of **1** with organolithium compounds, the reaction was tested at room temperature, using two different organolithiums. Under these conditions, branched hydrazines, **7**, can be obtained as shown in Eqn (4).



The addition of the R^1CH_2Li was carried out using slight excess of the reagent, and short reaction times (a few minutes, except in the case of MeLi, that required longer times). These are the conditions leading to the hydrazone, **2**. For the addition of the second organolithium, R^2Li, a higher excess was used (4–5 equivalents of reagent), and longer reaction times were needed (2 h). As can be observed in the Table 3, the yields of **7** are good but variable amounts of **2** remained. For a couple of two organolithiums, different products can be obtained depending on the *order* in which the two organolithiums were added. On the other hand, it can be observed that using PhLi, the corresponding hydrazine is not obtained (even if the reaction is carried out at 50 °C), this result is, likely, a consequence of the lower reactivity of PhLi, compared to the alkyllithium compounds. Consequently, the yield of denitrosation products increases considerably.

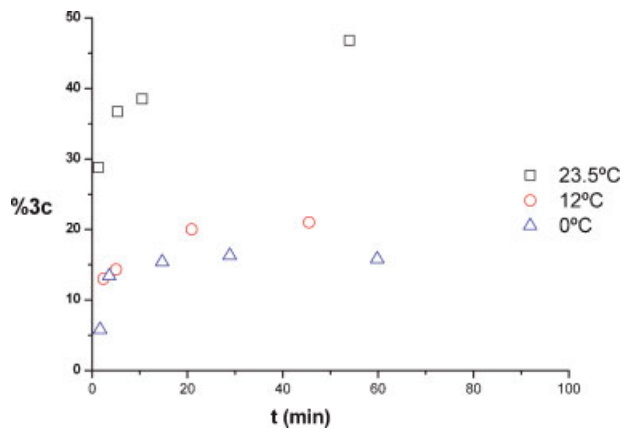
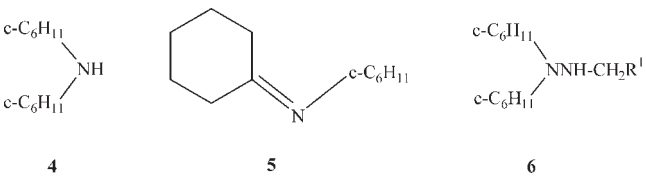


Figure 1. Reaction of dicyclohexylnitrosamine, **1**, with 3 equivalent BuLi in THF, at three temperatures. % yields of trialkylhydrazine, **3c**, as a function of the reaction time

Side products and mechanistic hints

For the study of a reaction mechanism, not only the main products are important, but the nature of the compounds that are produced by lateral reactions used to be significant. In all the above described reactions, some side products were also produced in variable amounts. To shed more light into the general mechanism of the global reaction mechanism, careful efforts were devoted to the isolation, characterization, and quantitative determination of the main side products. Those were identified as dicyclohexylamine, **4**, *N*-cyclohexylidenecyclohexylamine, **5**, and *N*,*N*,*N*′-dicyclohexylalkylhydrazines, **6**, which are shown below.



Variable small amounts of the corresponding dialkyl amine (such as **4**), were also detected in the reaction mixture, when nitrosamines were synthesized by the NO insertion into the N—Li bond of lithium amides, following the procedure previously reported.[18] The finding of this type of side product (i.e., dialkyl amines) under those reaction conditions could, in principle, be explained by small amounts of remaining lithium amide and/or by the reagent slight hydrolysis in the reaction flask. Nevertheless, in the present case, the reaction starts from pure (amine free) solid nitrosamine **1**. The appearance of **4** and **5** in the reaction mixture suggests the involving of some denitrosation process, likely occurring through a nitrosiminium ion intermediate stabilized by resonance, as shown in Scheme 1.

Denitrosation of *N*-nitroso-*N*-dialkylamines is a subject of active interest, since it is thought their carcinogenic and mutagenic activity to be due in part to the fact that they decompose to precursors of DNA-alkylating agents. Therefore, the solution chemistry of these substances is of considerable importance in understanding nitrosamine carcinogenesis. Fishbein and coworkers[25] reported the first evidence of *N*-nitrosiminium ions in the non-enzymatic decomposition of some α-acetoxy-*N*-nitrosodialkylamines. *N*-nitrosiminium ions are ambident electrophiles and can be trapped by special agents and solvents. Azide ion is known to be an efficient trap of some unstable cations, reacting with a diffusion-limited rate constant. The kinetic of the trapping of *N*-nitrosiminium ions by azide ions was reported, and it demonstrated that formation of the

Table 3. Reaction of dicyclohexylnitrosamine, **1**, with two different organolithium compounds in THF, at room temperature. Relative % yields of trialkyl hydrazines, **7** and side products[a]

Entry	RLi[b]	R^2Li	$[R^2Li]:[1]$	R^1	% 2[c]	%4[d]	%5[e]	%6[f]	% 7[g]
a	MeLi	*n*-BuLi	4	H	1	5	4	1	64[h]
b	*n*-PrLi	*n*-BuLi	5	Et	5	5	5	6	69
c	*n*-PrLi	*n*-$C_5H_{11}Li$	5	Et	2 (**2b**)	6	2	—	59[i]
d	*n*-BuLi	*n*-PrLi	5	*n*-Pr	9 (**2c**)	1	6	4	64
e	*n*-BuLi	PhLi	3	*n*-Pr	61 (**2c**)	14	16	7	—

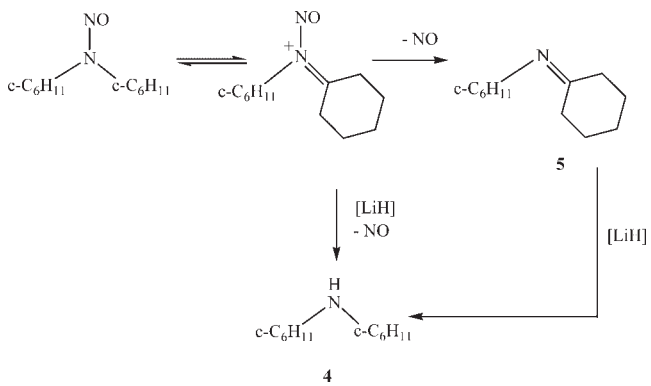
[a] Reaction time: 2 h.
[b] [RLi]:[**1**]:1.05–1.2.
[c] **2**: $(c\text{-}C_6H_{11})_2NN{=}CHR^1$.
[d] **4**: $(C_6H_{11})_2NH$.
[e] **5**: $C_6H_{11})N(C_6H_{10})$.
[f] **6**: $(C_6H_{11})_2NNHCH_2R^1$.
[g] **7**: $(c\text{-}C_6H_{11})_2NNH\text{-}CHR^1R^2$.
[h] 15% of **3c** determined.
[i] Side products 39% total yield.

N-nitrosiminium ion is a reversible reaction, as shown in Scheme 1.[26] Denitrosation of the *N*-nitrosiminium intermediate (giving **5**) and simultaneous reduction could be the route for formation of side products **4** and **5**.

Addition of RLi to the N=O bond

Though the reaction of organolithiums with the N=O bond is much less known than the synthetically very useful addition of RLi to C=O bonds, the efficient formation of hydrazones shown in the present study can be interpreted by an addition mechanism.

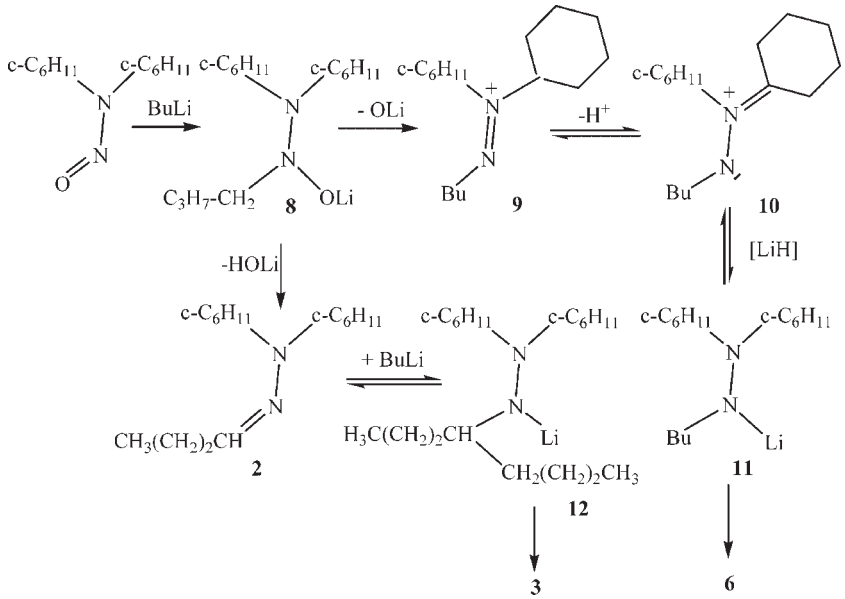
RLi reagents are known to have some reducing properties and one of the undesirable side reactions that usually occur in their additions to simple carbonyl compounds, is the production of alcohols and even hydrocarbons, from the reduction of the starting carbonyl substrate (probably through the elements of *lithium hydride*). Therefore, under the present conditions, the appearance of **6** in low variable yield could, in principle, be explained as the product resulting from of a hypothetic reduction of the hydrazones **2**. Formation of **3** could be a simple addition of another molecule of RLi to the double C=N. Addition of organolithium to C=N bond is less frequent than C=O bond, though it is a known reaction.



Scheme 1.

Nevertheless, in the present conditions, addition of a second molecule of RLi to C=N is much more difficult than to N=O. It takes much longer reaction times and never goes to completion. Addition of fresh RLi after the reaction has advanced produces some additional **3**, but not complete conversion of **2** could be afforded, even using relatively large excess of RLi. Similar results were recently reported for the addition of α-lithio methoxyallene to some hydrazones; surprisingly, no reaction was observed by using 2 M equivalents of the RLi. 6 M equivalents were required to engage completely the substrate, and variable amounts of hydrazone were recovered when intermediate quantities were used (no explanation was given).[19] These observations together with the fact that the kinetics of the reaction becomes much slower after a certain reaction time (see Fig. 1) suggest that some RLi could be involved in complexation of the N=C bond, or in another type of more complex equilibria as those previously observed in the insertion of CO into the N—Li bond of lithium amides.[21,24,27]

One of the first studies of reactions of organolithiums with nitrosamines reported variable products depending on the substituents in the nitrosamine and the nature of the organolithium, in most cases the yields were around 30% or below.[28] It was suggested that *azomethine* intermediates are formed and subsequently dimerize head to tail to form the isolated *sym*-hexahydrotetrazines. The authors' attempts to synthesize hydrazones were fully unsuccessful, and only in one case a trialkylhydrazine could be obtained. Thus, when *N*-methyl-*tert*-butylnitrosamine was treated with *tert*-butyllithium and quenched with ethanol 1,2-*tert*-butyl-1-(ethoxymethyl)hydrazine was formed.[28] This compound did not eliminate ethanol to form the *sym*-hexahydrotetrazine (as it was observed in the other cases), probably due to steric hindrance of the *tert*-butyl groups. Nevertheless, under the conditions of the present study, hydrazones could be isolated in good yields. *Azomethines* could also be suggested as likely intermediates in a complex reaction scheme as outlined in Scheme 2, which is consistent with the

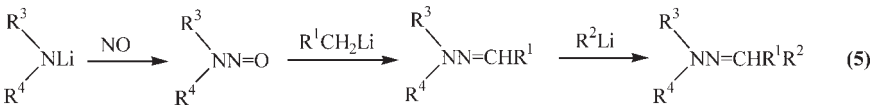


Scheme 2.

observed results for the formation of products **2, 3**, and **6**. Reactions of nitrosamines with Grignard reagents were previously studied, but the yields were not good, in some cases complex mixtures (as least 8 products) or tar products were obtained, even when the reactions were carried out at low temperatures; better results were obtained with organolithiums, but only in one case a good yield (80%) of the corresponding hydrazone was obtained.[23]

An alternative approach

The procedure herewith described, could be combined with the previously reported synthesis of *N*-nitrosamines from lithium amides and NO,[18] affording a very convenient and efficient tandem sequence for the synthesis of substituted hydrazones and trialkyl hydrazines from amines as illustrated schematically in Eqn (5).



The first step in the Scheme 2 involves attack by the organolithium reagent on the nitroso moiety to give adduct **8** which by elimination of the elements of HO^- Li^+ produces the hydrazone **2c**. In smaller amount, **8** could undergo similar elimination but involving the proton of the α-carbon of one of the cyclohexyl moiety, producing the azomethine **10**, (presumably through a diazenium salt **9**). In the presence of tiny amounts of LiH (an undesirable side product usually formed in the reactions of organolithium compounds) intermediate **10** could undergo *reduction* of the double bond forming **11** that on hydrolysis would produce the hydrazine **6** which was isolated in small amounts. By addition of a second molecule of RLi to the C═N bond the adduct **12** is formed, which after quenching produces the trialkylhydrazines **3**. Under these conditions, dimerization of the azomethine is avoided and several trialkylhydrazines could be obtained in good yields. As can be observed, some trialkylhydrazines exhibit chiral carbon; though the purpose of this paper is not synthetic, it is worthwhile to point out that, chiral hydrazines could likely be obtained by carrying our the reaction in the presence of a suitable chiral auxiliary. Examination of the potential utility of this new reaction is under progress.

Searching for an additional evidence for the suggested global mechanism, an alternative approach was examined. The *N*-dicyclohexylnitrosamine, **1**, was prepared by the NO insertion into the N—Li bonds of lithium *N*,*N*-dicyclohexylamide (as shown in the first step of Eqn (5)) by the procedure described in the experimental section, that afforded a quantitative conversion of the lithium amide to the corresponding nitrosamine. Thus, the reaction of lithium *N*,*N*-dicyclohexylamide with NO was carried out at −78 °C, at atmospheric pressure, when the absorption of NO ceased, BuLi (in 1–1.3 molar ratio) was added and 98% of the expected **2c** was obtained. Nevertheless, in a second approach, conditions were changed in this way; after the NO absorption was complete, the excess of NO was removed by vacuum out from the reaction flask, before adding 1–1.2 equivalents of *n*-BuLi. Under these conditions, dicyclohexylamine, **4**, was obtained in yields higher than 20%, and the yields of **2c** diminished significantly. If 5 equivalent of BuLi is added under these conditions, (to produce the corresponding **3c**), the amount of **4** amounts to 26%, after 2 h reaction, and the trialkyhydrazine is the only main product. This approach was also tested by using the more sterically hindered lithium cyclohexylisopropylamide in its reaction with NO. Under

Table 4. Reaction of NO with R^1R^2NLi in THF, followed by *in situ* reaction with *n*-BuLi[a]

R^1R^2NLi	BuLi (equivalent)	R^1R^2NH	% R^1R^2NNO	yields $R^1R^2NN{=}CHC_3H_7$	Hydrazine
$R^1 = R^2 = Cy$	1.1	21	34	44	—
$R^1 = R^2 = Cy$	5	26	4	5	50 (**3c**)
R^1 = i-Pr, $R^2 = Cy$	1.3	35	36	23	—
R^1 = i-Pr, $R^2 = Cy$	1.3	31	39	26	—
R^1 = i-Pr, $R^2 = Cy$	1.3	30	44	19	—

[a] Reaction with NO at temperatures in the range from −19 to –0 °C, and atmospheric pressure. The excess of NO was removed by vacuum before adding BuLi at room temperature.

regular conditions, the reaction of lithium cyclohexylisopropylamide with NO at room temperature rendered cyclohexylisopropylnitrosamine in 96% yield.[18] Nevertheless, it can be observed in Table 4, that by removing the excess of NO before adding the RLi, the yield of cyclohexylpropylamine was higher than 30% in the three cases, while the yields of the corresponding nitrosamine and hydrazone diminishes significantly. The reactions were repeated twice or thrice and it was observed that the yield of amine was somehow dependent on the amount of NO remaining in the reaction flask. This result is consistent with the equilibrium for the nitrosamine denitrosation, that is shown in Scheme 1.

Examination of a tandem sequence for a clean production of trialkylhydrazines, as shown in Eqn (5), is under progress. This new procedure would avoid the extra steps required by previous methods that use protecting groups and the selective cleavage of those for the synthesis of multisubstituted hydrazines.

CONCLUSIONS

The study of the reaction of dialkylnitrosamines with organolithium reagents allowed the development of a simple route for the synthesis of substituted hydrazones, and for the synthesis of multisubstituted hydrazines. Trialkyl hydrazines have acquired renewed interest for their wide versatile properties, and they can be formed by the one-pot one-step reaction studied in this paper. Some kinetic determinations, and the identification of lateral products carefully isolated in small amounts, suggested likely mechanistic routes that were confirmed by an alternative approach preparing the starting nitrosamines by the reaction of NO with lithium amides. If the excess of NO is removed before adding the organolithium, significant amounts of the corresponding dialkyl amine are determined in the reaction mixture, thus confirming that extensive denitrosation occurs under these conditions.

EXPERIMENTAL SECTION

WARNING: Most *N*-nitrosamines are powerful direct acting carcinogens, they have to be handled and disposed with special care avoiding skin contact. Manipulations were carried out using frequently changed double pairs of disposable gloves and in a well-ventilated hood. Contaminated materials were disposed in special containers for further disposition of the still potentially contaminated materials.

General remarks

All reactions involving organolithium reagents were carried out by standard techniques for the manipulation of air- and water-sensitive compounds, previously described.[29] The product identification was carried out by melting point (when available) and spectroscopic data. Product quantification was carried out by using a 5890 Series II Plus Hewlett-Packard gas chromatograph (equipped with a DB-5 column), at 70–280 °C programmed temperature. Mass spectra were recorded on a BG Trio-2 spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded in a Brucker 200 and in a Brucker 500 MHz NMR spectrometers.

Solvents and reagents

Hexane and THF (HPLC grade) were distilled from blue solutions of sodium-benzophenone ketyl immediately before using. *n*-BuLi (1 M in *n*-hexane solution) was synthesized as previously described, starting from *n*-butyl-chloride.[22] *n*-PrLi and *n*-pentyl Li (0.5 M hexane solutions) were prepared similarly to *n*-BuLi, starting from the respective alkylbromides. Solid MeLi was prepared from metal-halogen exchange, starting from *n*-BuLi (5 mmol) and 0.62 ml of MeI (5 mmol) was added in several aliquots, at 0 °C. The precipitated MeLi was centrifugated, the solution was removed, and the white crystals were washed thrice with 3 ml of anhydrous hexane followed by centrifugation each time. The resulting solid was dried under vacuum at room temperature, and dissolved in THF immediately before to use. Solid PhLi was prepared from metal-halogen exchange, by the same procedure described for MeLi, 1.2 ml of PhI (5.25 mmol) replacing the MeI. All organolithiums reagents were titrated with the double titration method, previously described.[30] *N*-nitrosodicyclohexylamine was synthesized by the general procedure developed by Zolfigol and cow, based on the *in situ* generation of NOCl by the reaction of $ZnCl_2$ and $NaNO_2$, in CH_2Cl_2, in the presence of wet SiO_2.[30] It was purified by crystallization from ethanol–water and washed with cold ethanol (mp = 104–105 °C).[18] The compound was kept under vacuum overnight prior to use.

Reactions of *N*-nitrosodicyclohexylamine with organolithium compounds

Synthesis of hydrazones ***2***: 210 mg (1 mmol.) of *N*-nitrosodicyclohexylamine, **1**, was put in a 10 ml round bottomed flask, equipped with a magnetic stirrer and protected from light by aluminum paper. The flask was tapped with a rubber septum, it was placed in a bath at the desired temperature, and then evacuated and filled with dry N_2, alternatively several times. Anhydrous THF of 2 ml of was added to dissolve the nitrosamine. Then the organolithium solution (1.05–1.2 mmol in *n*-hexane) was added by syringe with vigorous stirring, and allowed to react for nearly 5 min. When MeLi is used, the reaction time should be approximately 2 h. Then, the flask was placed in a water–ice bath, and distilled methanol (*ca.* 0.15 ml) was syringed. The solvent of the resulting mixture was distilled at reduced pressure, obtaining an oil. Upon purification by silica-gel column, pure hydrazones are obtained as pale yellow oils. For quantification, the crude mixture is dissolved in CH_2Cl_2 and filtered, prior to CG-analysis.

Synthesis of hydrazines ***3*** *and* ***7***: the procedure is similar to the hydrazone synthesis, but using 4–5 equivalents of organolithium reagent, and allowing a reaction time for 2 h at room temperature. When two different organolithiums are used, the first one is added in a small excess (1–1.2 mmol, as previously described for hydrazone synthesis), and the second (3–5 equivalents) is added later (after 5 min), allowing to react for 2 h and then distilled methanol (0.75 ml) is syringed. Upon purification by chromatographic column, pure hydrazines are obtained as air-sensitive pale yellow oils. For quantification, the crude mixture is dissolved in CH_2Cl_2 and filtered, prior to CG-analysis.

Kinetic study of the reaction of ***1*** *with n-BuLi*: The reaction of **1** with BuLi was carried out at three working temperatures (0 °C, 12 °C and room temperature), following the conditions described for the hydrazine synthesis ([*n*-BuLi]:[**1**] = 3). Aliquots of *ca.* 0.5 ml were withdrawn by a syringe at different time intervals, and quenched with distilled MeOH (30 μl) in small vials, that had been previously evacuated and purged with N_2. The resultant solutions were analyzed by GC.

Reaction of lithium dialkylamides with NO. Typical reaction conditions are described for lithium dicyclohexylamide. A round-bottomed reaction flask containing a teflon-coated stirring bar and capped with a no-air stopper was evacuated and filled with dry nitrogen alternatively several times, and then nitric oxide was added at *ca.* 1013 mbar. After that, a solution of lithium dicyclohexylamide (1 mmol) in THF (1 ml) was added with vigorous magnetic stirring, for 3 h. The initial colorless solution turned to orange at the beginning, and this color stayed along the reaction. The reaction was worked out with 0.2 ml of distilled methanol. Excess NO was removed and distilling the THF under reduced pressure afforded slightly orange crystals of **1** in a quantitative yield. Crystallization from acetone rendered white crystals of m.p. 104.5–105–5 °C.

SUPPORTING INFORMATION

All the compounds herewith described were fully characterized by ^{1}H- and ^{13}C–NMR and MS spectroscopy. The data corresponding to every compound are provided as supplementary material.

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